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ORIGINAL ARTICLE

Major bleeding risk associated with oral anticoagulant in real clinical practice. A multicentre 3-year period population-based prospective cohort study

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Aims: The objective was to compare major bleeding risk of direct oral anticoagulants (DOACs; per type and dose) with vitamin K antagonists (VKAs), irrespective of indication, using real-world data.

Methods: A population-based prospective cohort study, using the French national health data system (SNIIRAM), identified 47 469 adults living within 5 well-defined geographical areas, who were new users of oral anticoagulants in the period 2013–2015: 20 205 VKA users, 19 579 rivaroxaban users, 4225 dabigatran users and 3460 apixaban users. From all emergency departments within these areas, clinical data for all adults referred for bleeding was collected and medically validated. The databases were linked for common key variables. The main outcome measure was major bleeding: intracranial haemorrhage, major gastrointestinal bleeding and other major bleeding events. Hazard ratios were derived from adjusted Cox proportional hazard models. We used propensity score weighting as a sensitivity analysis, with separate analyses according to indications (atrial fibrillation or venous thromboembolism).

Results: Compared to VKAs, high and low-dose DOACs were associated with a reduced risk of intracranial haemorrhage (adjusted hazard ratio 0.55, 95% confidence interval 0.37–0.82 and 0.54, 0.26–1.12 respectively), and a reduced risk of other major bleeding events (0.41, 0.29–0.58 and 0.41, 0.22–0.79 respectively), irrespective of duration and indication. Neither DOAC dose evidenced any significant difference from VKAs in terms of risk of major gastrointestinal bleeding.

Conclusion: There is a clear benefit of using DOACs with regard to intracranial haemorrhage. The study provides new insight into major gastrointestinal and other major bleeding events.

KEYWORDS

major bleeding, oral anticoagulant, real-world data

The authors confirm that the Principal Investigator for this paper is Jacques BOUGET and that he had direct clinical responsibility for patients.

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1 | INTRODUCTION

Anticoagulants have demonstrated significant benefits in preventing venous or arterial thrombotic events, especially for stroke, atrial fibrillation (AF), venous thromboembolism (VTE) and in presence of mechanical heart valves.[1] These drugs are commonly prescribed, and their long-term use has been on the increase, particularly among the elderly.

Bleeding is the most well-known and feared complication of anticoagulants. Numerous studies on drug-induced adverse events have reported anticoagulants as the first medication class involved in resort to emergency departments and hospitalization among adults,[2] mostly for haemorrhage, and particularly intracranial haemorrhage (ICH), which results in substantial morbidity and mortality.[3]

Direct oral anticoagulants (DOACs), including direct thrombin inhibitors and factor Xa inhibitors, are now available for the prevention of stroke and systemic embolism. Pivotal randomized clinical trials (RCTs) have reported a very considerable reduction in the relative risk of ICH, ranging from 23% for **rivaroxaban**[4] to almost 70% for **dabigatran etexilate** 110 mg twice daily.[5] Major gastrointestinal (GI) bleeding under DOACs has been either as frequently observed as with **warfarin**[5,6] or more frequently observed[4,5] than with warfarin.

Real-world data on bleeding risk are needed, particularly as the selection criteria applied to RCTs may have artificially improved the picture. Trial patients often have a lower risk of bleeding than do those in ordinary practice, because trials often exclude patients with the highest risk. It is important to know whether the bleeding event rates observed in RCTs are reflected in routine clinical practice, and whether there are differences across the different DOACs for bleeding risk.

Several analyses using large reimbursement claims databases have yielded reassuring findings in line with those from RCTs: a lower rate of ICH with both doses of dabigatran,[7–18] with rivaroxaban[16,18–20] and with **apixaban**,[13,16,18,20] similar[7,8,10,11,14,17,18] or higher rates of GI bleeding associated with dabigatran[7–9,12,13,21] or rivaroxaban[18,22] compared to warfarin; and lower rates of GI bleeding associated with apixaban.[13,18] Data on dabigatran from the USA are also reassuring, bearing in mind that the Food and Drug Administration has not authorized the 110-mg dose for AF patients.[10,12,17,21,23–27]

Meta-analyses[28–31] of these observational studies on real-world data, mostly based on reimbursement claims, concluded heterogeneity across studies. Assessing bleeding from reimbursement claims is liable to be influenced by variability in coding and misclassification, which could bias relative risk estimates. In addition, most studies focused on patients with nonvalvular AF. Only 3 studies have provided data for a wider population.[23,25,32]

We conducted a population-based cohort study within well-defined areas, including new users of oral anticoagulants, collecting data prospectively and medically validating all major bleeding events over a 3-year period. Our main objective was to compare major bleeding risk per type and dose of DOACs with VKAs, whatever the indication.

What is already known about this subject

- Meta-analyses of randomized trials have identified higher rates of gastrointestinal bleeding for direct oral anticoagulant (DOACs) compared to warfarin.
- All DOACs significantly reduce the risk of intracranial bleeding compared to adjusted-dose warfarin.
- Observational studies on real-world data, mostly based on reimbursement claims, have been inconsistent and generally imprecise.

What this study adds

- This study included new users of oral anticoagulants, irrespective of indication, thus broadening the view on safety issues.
- The medical validation of all bleeding events supports the validity of the results.
- DOACs were associated with a decreased risk of other (nongastrointestinal nonintracranial) major bleeding events among patients, irrespective of duration, dose and indication, compared to vitamin K antagonists.

2 | METHODS

2.1 | Study design and participants

We conducted a prospective population-based cohort study using the French national health insurance database (SNIIRAM). We were provided access to a subset of all adult subjects (>18 years) living within 5 well-defined areas, with at least 1 reimbursement for an oral anticoagulant (dabigatran, rivaroxaban, apixaban or VKA) in 2013–2015. To medically validate all bleeding events occurring in this cohort, we linked these individuals to an *ad hoc* data collection from all emergency departments, either public or private, located in these 5 areas. The areas were defined using lists of postcodes around 5 large French cities (Angers, Brest, Grenoble, Nantes and Rennes, all with a university hospital, covering slightly more than 3 million inhabitants). This list comprises all municipalities in which inhabitants are referred in case of need to 1 of the participating emergency services. The study received regulatory approval (CNIL, DR-2013-488, with subsequent substantial changes DR-2016-489).

Firstly, the SNIIRAM anonymously and comprehensively links a healthcare reimbursement database (DCIR) to the French hospital discharge database (PMSI): the DCIR contains anonymous individual data on all reimbursements for health expenditure, including drugs; the database does not provide any direct information on the medical indication for each reimbursement; the PMSI provides hospital discharge diagnoses (ICD-10 code) as well as details of medical acts.

Secondly, an *ad hoc* data collection from emergency departments gathered clinical data for all adult subjects referred for bleeding between 1 January 2013 and 31 December 2015, focusing on oral anticoagulants, the type of bleeding, and also collecting demographics (month and year of birth, sex) and date of hospital admission. To identify patients referred for bleeding, the first step was a search based on carefully-chosen haemorrhage-related diagnostic codes or the implementation of specific emergency therapies (red blood transfusion, platelet transfusion, vitamin K, protamine sulfate, prothrombin complex concentrate and FEIBA). This search was applied to the electronic health records from emergency departments. A pilot study found good sensitivity for the computer search.[33] In each area, a referent expert medical doctor checked all records identified for oral anticoagulant exposure and severe bleeding criteria (see below for details).

Thirdly, the SNIIRAM sample and the *ad hoc* data collection sample were linked using common key variables (date of birth [month, year], sex, date of hospital entry and discharge, type of oral anticoagulant, and care facility involved). Pairs were defined from emergency department stays identified in the SNIIRAM subset, matched on the key variables to a bleeding event in the *ad hoc* data collection (see reference [34] for matching details).

2.2 | Outcomes

We anticipated that the estimates for associations between anticoagulant and major bleeding could be heterogeneous across the 3 types of major bleeding, and we therefore defined 3 classes for the primary outcome: ICH, GI bleeding and other major bleeding events. Major bleeding was defined from at least 1 of the following criteria: unstable haemodynamics (systolic arterial pressure <90 mmHg or mean arterial pressure <65 mmHg) or haemorrhagic shock, uncontrollable bleeding, need for transfusion or haemostatic procedure (embolization, endoscopic procedure, surgery). The location or the symptoms then defined the type: ICH for intracranial haemorrhage, acute GI bleeding, and other major bleeding in life-threatening locations—intraspinal, intraocular, retroperitoneal, pericardial, thoracic, intra-articular or intramuscular haematoma with compartment syndrome. We also considered epistaxis with at least 2 procedures of nasal packing, and haematuria when bleeding lasted >12 hours despite bladder washing as *other* major bleeding events. There was a slight alteration with respect to the International Society on Thrombosis and Haemostasis classification of major bleeding events[35] because in our dataset no information was available on haemoglobin levels.

The secondary outcome was all-cause mortality.

2.3 | Main exposure: oral anticoagulant

Only *new users*, defined as having had no oral anticoagulant exposure in 2012, were analysed.

The indication for anticoagulant prescription was derived from the main discharge diagnosis and/or medical acts performed in the 30 days before the first observed issue of anticoagulant (Table S1 for code definitions). *Medical acts* include imagery procedures such as Doppler ultrasonography (of the lower limb for a suspicion of deep vein thrombosis, echocardiography), computed tomography scan, magnetic resonance imaging; and therapeutic procedures (thrombectomy, fibrinolysis, thrombo-aspiration, transcutaneous cardio-version, plaster cast, osteosynthesis, orthopaedic surgery, valve surgery, vascular bypass, angioplasty, coronary surgery).

For patients who were not hospitalized and had no *medical act* within a month of the start of OACs, the indication was not determined and classified as *unknown*. For the at-risk cohort identified through the SNIIRAM database, we classified person–month exposure to dabigatran, rivaroxaban, apixaban or VKAs on the basis of their issue dates. Exposure groups and index dates were defined at first dispensation. We differentiated high-dose (dabigatran 300 mg or rivaroxaban 15 or 20 mg or apixaban 10 mg/d) and low-dose (dabigatran 220 mg or rivaroxaban 10 mg or apixaban 5 mg/d). For DOACs, they are prescribed at fixed doses and the quantity dispensed by pharmacists is limited by law to 30 days, so the number of days of supply was established as [last issue date minus first issue date] plus 30 days. For VKAs, computing supply was not straightforward as we lacked information on dosing instructions. The number of days of supply was established as [last issue date minus first issue date] plus 60 days; we checked that there was at least 1 INR measure within the previous 2 months.

Patients were censored in case of: discontinuation of oral anticoagulants (using the end date of supply as previously described) or switch (from VKAs to DOACs or vice versa); date of dose change for DOACs (from high-dose to low-dose or vice-versa); death; major bleeding event (as previously defined); or moving outside the area; or end of follow-up, whichever occurred first.

The main exposure was further subdivided according to whether the anticoagulant drug was prescribed alone or in combination with an antiplatelet drug (**aspirin**, **clopidogrel**, **ticagrelor** or **prasugrel**) and according to the duration of use (under 6 months, 6 to 12 months or over 1 year).

2.4 | Statistical analysis

Patient characteristics and descriptive incidence rates were explored first. Comorbidities (Table S1 for code definitions) and comedication (listed in Table 1) were retrieved from SNIIRAM. We calculated a modified HAS-B(L)ED score (adapted from Pister et al.[36]) as a measure of bleeding risk and a comorbidity score (Charlson's index adapted by Bannay et al., [37] see Tables S2 and S3 for definitions of scores). Crude incidence rates were calculated for the first bleeding episode per 10 000 person–months according to the type of bleeding, the type of oral anticoagulant (VKAs, DOAC high-dose or DOAC low-dose), and the duration of use (under 6 months, 6 to 12 months or over 1 year) and the HAS-B(L)ED score level.

Cox proportional hazard regression analyses were conducted for each type of bleeding event to determine hazard ratios for

TABLE 1 Characteristics of subjects by drug exposure

Characteristics	VKA *n* = 20 205	Dabigatran low *n* = 2944	Dabigatran high *n* = 1281	Rivaroxaban low *n* = 5246	Rivaroxaban high *n* = 14 333	Apixaban low *n* = 1415	Apixaban high *n* = 2045
Age, median (IQR)	77 (64–85)	76 (65–83)	67 (60–74)	68 (60–76)	69 (58–79)	82 (74–86)	72 (64–78)
>65 y	14 616 (72.3)	2200 (74.7)	744 (58.1)	3028 (57.7)	8542 (59.6)	1224 (86.5)	1473 (72.0)
Sex, female	10 354 (51.2)	1533 (52.1)	445 (34.7)	2892 (55.1)	6451 (45.0)	825 (58.3)	751 (36.7)
Presumed indication[a]							
AF or peripheral embolism or stroke	11 535 (57.1)	1275 (43.3)	946 (73.8)	242 (4.6)	7774 (54.2)	913 (64.5)	1820 (89.0)
VTE	5662 (28.0)	-	53 (4.1)	-	4598 (32.1)	-	67 (3.3)
Lower limb orthopaedic surgery	218 (1.1)	1138 (38.7)	-	4371 (83.3)	-	320 (22.6)	-
Valvular heart disease	406 (2.0)	-	5 (0.4)	-	28 (0.2)	1 (0.1)	6 (0.3)
Other or unknown	2384 (11.8)	531 (18.0)	277 (21.6)	633 (12.1)	1933 (13.5)	181 (12.8)	152 (7.4)
Comorbidities [b]							
Diabetes mellitus	3204 (15.9)	327 (11.1)	178 (13.9)	503 (9.6)	1564 (10.9)	194 (13.7)	333 (16.3)
Coronary heart disease	2451 (12.1)	131 (4.4)	65 (5.1)	104 (2.0)	595 (4.2)	123 (8.7)	126 (6.2)
Haematological or immune disease	1581 (7.8)	69 (2.3)	14 (1.1)	147 (2.8)	301 (2.1)	55 (3.9)	40 (2.0)
Medication use							
Lipid-lowering drug (last year)	8471 (41.9)	1135 (38.6)	466 (36.4)	1607 (30.6)	4718 (32.9)	567 (40.1)	949 (46.4)
Antiulcer agent (last year)	10 626 (52.6)	1434 (48.7)	496 (38.7)	3291 (62.7)	6045 (42.2)	707 (50.0)	856 (41.9)
Antiplatelet agents (recent use)	6320 (31.3)	847 (28.8)	365 (28.5)	723 (13.8)	3579 (25.0)	536 (37.9)	729 (35.6)
NSAID (last year)	5000 (24.7)	1117 (37.9)	455 (35.5)	3341 (63.7)	4841 (33.8)	395 (27.9)	552 (27.0)
Modified HAS-B(L)ED score[c]							
0–1	8151 (40.3)	1399 (47.5)	751 (58.6)	2956 (56.3)	8614 (60.1)	547 (38.7)	1037 (50.7)
2	6,661 (33.0)	1068 (36.3)	392 (30.6)	1560 (29.7)	4109 (28.7)	585 (41.3)	750 (36.7)
≥3	5393 (26.7)	477 (16.2)	138 (10.8)	730 (13.9)	1610 (11.2)	283 (20.0)	258 (12.6)
Concomitant medications [d]							
Antiplatelet agents	5218 (25.8)	503 (17.1)	194 (15.1)	719 (13.7)	1848 (12.9)	241 (17.0)	265 (13.0)
NSAID	1549 (7.7)	394 (13.4)	187 (14.6)	1736 (33.1)	1683 (11.7)	132 (9.3)	143 (7.0)
Modified Charlson comorbidity index[e]							
0	10 060 (49.8)	2105 (71.5)	937 (73.1)	4410 (84.1)	10 629 (74.2)	870 (61.5)	1379 (67.4)
1–2	6244 (30.9)	617 (21.0)	275 (21.5)	721 (13.7)	2867 (20.0)	392 (27.7)	512 (25.0)
3–4	2705 (13.4)	182 (6.2)	63 (4.9)	78 (1.5)	593 (4.1)	121 (8.6)	118 (5.8)
≥5	1196 (5.9)	40 (1.4)	6 (0.5)	37 (0.7)	244 (1.7)	32 (2.3)	36 (1.8)

Values are *n* (%) unless stated otherwise; high: dabigatran 300 mg or rivaroxaban 15 or 20 mg or apixaban 10 mg/d; low: dabigatran 220 mg or rivaroxaban 10 mg or apixaban 5 mg/d.

[a]based on hospital discharge main diagnosis (according to ICD-10 or medical act classification in the month before the index date;

[b]based on hospital discharge diagnosis (according to ICD-10)z or comedications (ATC system) in the previous year, see Table S1 for details;

[c]The HAS-BLED score assigns points for the presence of hypertension, abnormal renal or liver function, stroke, bleeding history, age 65 years or older, and antiplatelet drug or alcohol use. Labile INR was excluded from our scoring; see Table S2 for details;

[d]at least 1 delivery concomitant with any anticoagulant;

[e]as defined by Bannay et al.,[37] see Table S3 for details; recent use was defined by at least 2 deliveries in the 3 months before index date.

AF, atrial fibrillation; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; VTE, venous thromboembolism

DOACs (high or low dose) *vs* VKAs, both unadjusted and adjusted on known patient characteristics: sex, modified HAS-B(L)ED score, and comorbidities using the modified Charlson index. For each particular type of bleeding event, censoring occurred when death or any other type of bleeding event occurred, whichever was first.

For each outcome we tested interactions between exposure and sex, modified HAS-B(L)ED score (<2, 2 and ≥ 3), and the modified Charlson index (4 classes). We also tested interaction with time. Subgroup analyses were performed for some components of the HAS-BLED score: firstly, a concomitant antiplatelet regimen defined as any antiplatelet agents dispensed at least once concomitantly with oral anticoagulant after the index date, and secondly age (under or over 65 years).

As a secondary analysis, Cox proportional hazard regression models were run to estimate overall survival for DOACs (high or low dose) *vs* VKAs.

We conducted 4 sensitivity analyses to assess the robustness of our findings. First, we restricted the study population to patients without a presumed orthopaedic indication and ran the same Cox model used in the main analysis. Second, we performed separate analyses for the 2 main indications, AF or stroke, and acute venous thromboembolism. We regenerated the probability of treatment, DOACs (high or low dose) *vs* VKAs in the AF or stroke population, and DOACs (high dose) *vs* VKAs in the acute venous thromboembolism population using logistic regression models (a multinomial regression in the AF or stroke population) using 22 prespecified variables (listed in Tables S4 and S5 along with standardized differences). We then used the stabilized inverse probability of treatment weighting based on the propensity score[38] as weights in Cox proportional hazard regression models. The weights were truncated by resetting the value of weights greater (or lower) than the 99th (1st) percentile to the value of the 99th (1st) percentile.[39]

Covariate balance between the weighted cohorts was assessed using standardized mean differences. To estimate the impact of absolute risks, we calculated the numbers needed to harm using weighted hazard ratios.[40] Third, adjusted Cox proportional hazard regression models were run to compare different DOACs, using apixaban as a reference. Fourth, we identified any hospitalization that occurred outside the prespecified area, with ICD-10 codes as primary discharge diagnoses that could be related to major bleeding, using a published list[41]: indeed, some subjects can experience bleeding while on holiday or travelling (i.e. only temporarily outside the area), and therefore their bleeding event cannot be medically validated from chart review. Cox proportional hazard regression analyses were run using a modified dataset including these events. All statistical tests were 2-tailed and *P*-values <.05 were considered significant. Statistical analyses were performed using SAS software 9.4 (SAS Institute, Cary, NC, USA). Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | Cohort characteristics

A cohort generation flowchart is presented in Figure 1: 47 469 patients who had started anticoagulants between 2013 and 2015 (new users) were eligible for inclusion. Baseline characteristics in relation to the type of oral anticoagulant first prescribed are presented in Table 1. The mean age was 70 years (median, 73 years, interquartile range, 62–82) and 51% were males. In all, 52% were diagnosed with AF, leaving 48% of the patients prescribed anticoagulants for other indications: mostly a diagnosis of VTE (22%) or VTE prevention following lower limb orthopaedic surgery (13%).

Patients treated with rivaroxaban or dabigatran at high doses were younger, and more likely to be male. Patients treated with any of the DOACs, whatever the dose, had lower comorbidity (modified Charlson index) and bleeding risk (modified HAS-B(L)ED) than patients treated with VKAs.

The median follow-up time was different between VKA, 234 days (interquartile range: 116–510), high-dose DOAC, 163 days (67–412) and low-dose DOAC, 60 days (60–119).

The moment of censoring and the numbers and reasons involved are described in Figure S1 and Table S6.

The end of follow-up and treatment discontinuation were the most common reasons for censoring. End of follow-up was the first reason among apixaban users (74% for high dose and 62% for low dose), which could be explained by the fact it was the last to join the market. Discontinuation ranked ahead of end of follow-up for low-dose dabigatran and low-dose rivaroxaban; this is intuitive, as low doses are associated with short-term treatment.

Differences in follow-up or treatment discontinuation timing across anticoagulant classes could bias estimates if there was an interaction with time. We checked for an interaction of this nature and did not detect any significant interaction.

We observed that switching and dose change (for DOACs) were uncommon except for high-dose dabigatran.

Lower limb orthopaedic surgery was the presumed indication observed for 5,829 (60%) out of 9605 patients with low-dose DOAC. In this context, the duration of treatment is short (2 weeks for knee replacement and 5 weeks for hip replacement).

3.2 | Incidence rates

A total of 573 (1.2%) patients experienced a first major bleeding episode. The fatality rate was 56/573 = 9.77%. Table S7 shows the number of bleeding events according to bleeding site and indication (A), and anticoagulant drug (B). Nearly all major bleeding events (98%) occurred among patients for whom an anticoagulant was prescribed for AF or VTE.

The crude incidence rates for all major bleeding were higher during the first 6 months of therapy than during the 6–12 months period,

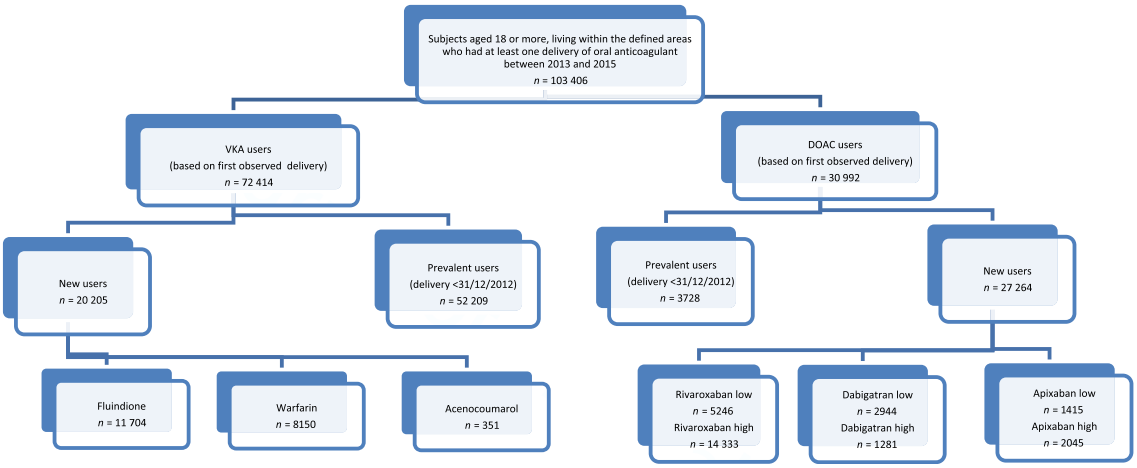

FIGURE 1 Study population

overall (Figure S2). There was a statistically significant linear association between HAS-B(L)ED and all major bleeding.

Among VKA users, the rates were higher for all bleeding sites, with higher HAS-B(L)ED scores (Table S8). Incidence rates for ICH and other major bleeding events were lower among DOAC users than VKA users irrespective of the DOAC dose (high or low).

We also observed 2196 deaths. The incidence rate per 100 person-years (95% confidence interval) was 9.05 (8.63–9.49) for VKA, 2.25 (2.01–2.51) for high-dose DOAC and 4.28 (3.71–4.94) for low-dose DOAC.

3.3 | Bleeding risk and anticoagulant exposure

Forest plots showing adjusted hazard ratios (HRs) for each first bleeding episode and all-cause mortality for DOACs compared to VKAs are presented in Figure 2. There were no interactions for any bleeding outcome between anticoagulant exposure and sex, modified HAS-B(L)ED score, or modified Charlson's index. The tests for interaction with time were all nonsignificant ($P > .15$). Proportional hazard assumptions held true. All results were therefore derived from Cox multivariate proportional models including sex, modified HAS-B(L)ED score, and

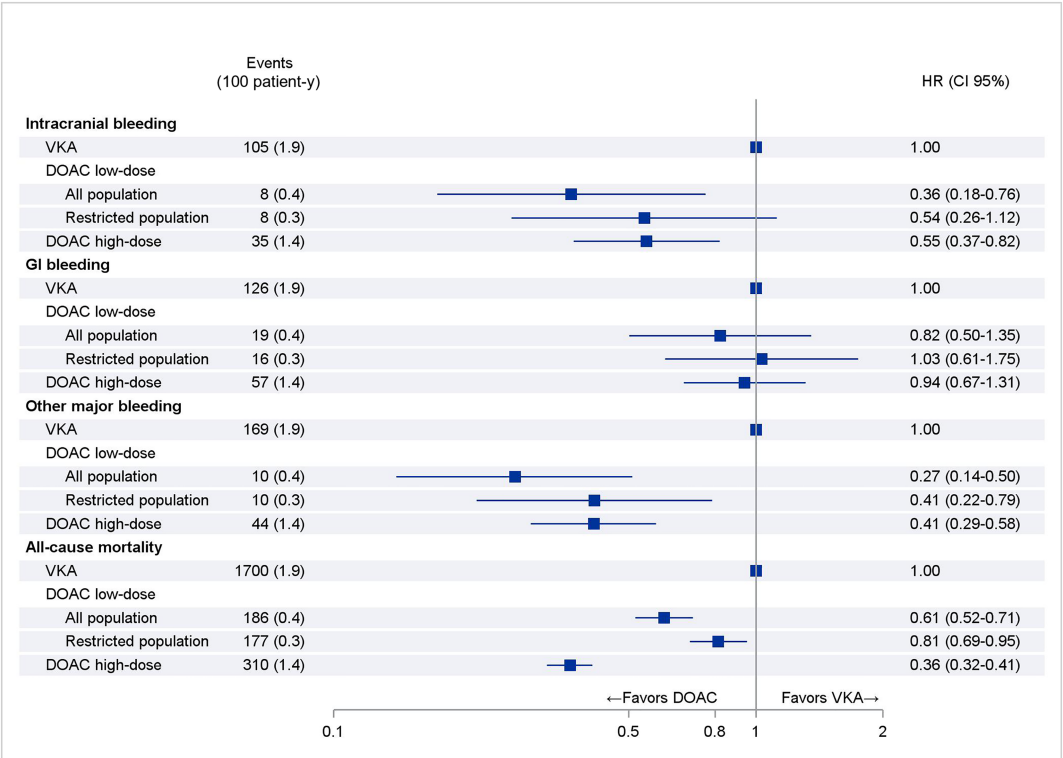

FIGURE 2 Association estimates between each major bleeding event, all-cause mortality, and direct oral anticoagulant (DOAC) compared to vitamin K antagonist (VKA). CI, confidence interval; GI, gastrointestinal; HR, hazard ratio

modified Charlson's index. Compared to VKAs, DOACs, either high or low-dose, were associated with a reduced risk of ICH and other major bleeding events, as well as with all-cause mortality. We observed consistent results across the different types of other major bleeding events (Figure S3). There was no obvious heterogeneity across the different types of DOACs in relation to any major bleeding outcome, or all-cause mortality (Figure S4). There was no statistically significant association between DOACs (whether low or high-dose) and major GI bleeding compared to VKAs (Figure 2 and S5).

There were no relevant interactions for any bleeding outcome or for all-cause mortality between anticoagulant exposure and concomitant antiplatelet drug use or age (elderly people >65 years, HASB(L) ED score level; data not shown).

3.4 | Sensitivity analyses

The results of the sensitivity analyses are summarized in Figures 2, 3 and S6. Restricting the study population to patients without presumed orthopaedic indications led to estimates close to null, but still statistically significant for other major bleeding and all-cause mortality; very few events were lost (3 GI bleedings and 9 deaths) but person-time at risk decreased by 30% (Figure 2). Analyses were then conducted in subcohorts of new anticoagulant users with AF (n = 24 505) or VTE (n = 10 380). Using the stabilized inverse probability of treatment weighting, the weighted cohorts were well balanced across all covariates (Tables S4 and S5).

Forest plots showing the weighted HRs for each bleeding event and all-cause mortality for DOACs compared to VKAs, are provided in Figure 3. Among patients with AF, DOACs were associated with a lower risk of other major bleeding events, and better overall survival than VKAs. Neither dose showed significant differences from VKAs in terms of ICH risk or GI bleeding risk. The same pattern was observed among patients with VTE.

Forest plots showing adjusted HRs for all-cause mortality for dabigatran, rivaroxaban or VKAs, using apixaban as a reference, are provided in Figure S6. Among patients with AF, high-dose apixaban was associated with better overall survival than VKAs and rivaroxaban.

A re-analysis including 93 major bleeding events occurring outside the study region did not change the hazard ratios (data not shown).

3.5 | Numbers-needed-to-harm

Figure S7 shows the numbers-needed-to-harm to assess the risk of DOACs in comparison with VKAs. Overall, the number-needed-to-harm (to observe 1 extra ICH or any other major non-GI bleeding event) remained fairly high.

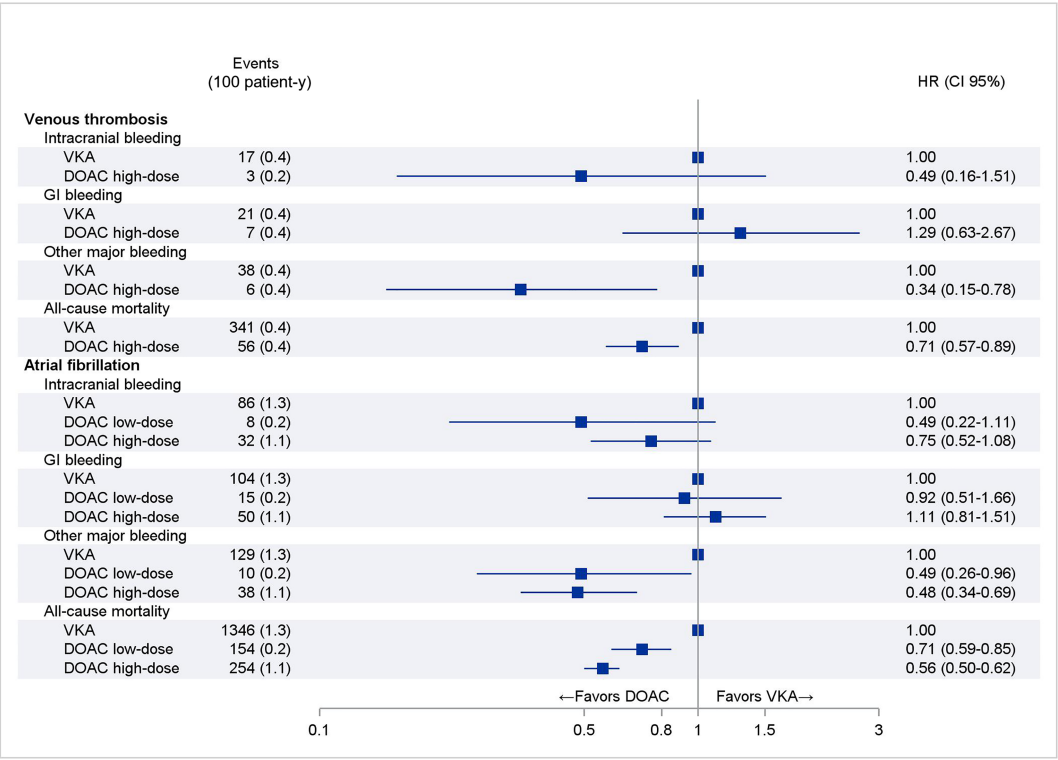

FIGURE 3 Association between each major bleeding event, all-cause mortality and direct oral anticoagulant (DOAC) compared to vitamin K antagonist (VKA) for venous thromboembolism or stroke prevention with atrial fibrillation. CI, confidence interval; GI, gastrointestinal; HR, hazard ratio

4 | DISCUSSION

This population-based cohort study was based not only on an administrative healthcare database, but also on a prospective clinical data collection with medical validation of all bleeding events. It showed a decreased risk of ICH, other major non-GI bleeding events, and all-cause mortality associated with the use of DOACs, whether low or high dose, irrespective of duration and indication, compared to VKAs. Neither DOAC dose differed significantly from VKAs in terms of GI bleeding risk. Among patients with AF, high-dose apixaban was associated with better overall survival than VKAs or rivaroxaban. Our findings for new anticoagulant users generally, whatever the indication, provide more generalizable evidence than findings from subsets of patients with only AF or VTE.

Our large comprehensive study is unique in its ability to directly compare different DOACs, including the different doses, encompassing all indications, in the exploration of an important and common safety outcome. This minimizes a bias that affects the external validity of studies focusing on hospital data only, whereby patients diagnosed and managed in primary care are not included. Indeed, roughly the same numbers of patients without AF are also prescribed anticoagulants (note the 48% in our study). We thus enhanced representativeness. We hypothesized that bleeding risk related to oral anticoagulants was mostly related to patient characteristics, not to the indication for anticoagulant use.

The other strength of our study is that it retrieves and links data from a prospective multicentre clinical study and data from a public healthcare system database that covers all residents within the defined area. As a result, the overall dataset gave us a complete picture of all hospitalizations and prescriptions dispensed, as well as the medical validation of bleeding events. On the one hand, this complete data coverage within the defined area eliminates a potential selection and recall bias, which is a problem in hospital-based observational studies; on the other hand, the clinical data enhance the validity of outcome measurements, minimizing classification bias, which is a problem in administrative databases. There is indeed a risk of misclassification related to coding errors at the time of hospital admissions; this may not be very likely for serious conditions like bleeding. However, the absence of validation could lead to overestimating incidence rates for major GI bleeding or urogenital bleeding.[42]

We adopted a new-user design capturing all events after the start of treatment. We ran a Cox proportional hazard model as the main analysis, adjusting for all available confounding factors, and we also undertook a sensitivity analysis using stabilized inverse probability of treatment weighting using a propensity score, which showed similar results.

Exposure in our study was based on reimbursement claims data. We studied drug exposure on the basis of pharmacy dispensations but had no information on patients' actual intake. The lack of information on patient adherence could have led to incorrect estimations of exposure, but the clinical validation of major bleeding made it possible to check that patients were still receiving anticoagulants at the time of bleeding.

Bleeding events could be more likely to be detected among patients prescribed VKAs than among those taking DOACs, introducing a surveillance bias, because of the regular monitoring required for VKA users. As major bleeding requires hospital referral, it is less likely to be missed among patients taking DOACs. This limitation does not apply to deaths.

Although we extensively adjusted for baseline differences, which should have helped to reduce the possible indication bias, it is unlikely that we captured the full extent of different prescribing behaviours, and some unmeasured, residual confounding factors could still be present. Our study lacked certain patient characteristics (such as smoking and weight, but we think they are not really confounders), or time-within-therapeutic-range for patients receiving VKAs.

Covering all indications and also including patients who received low-dose DOAC for brief thromboprophylaxis after orthopaedic surgery may have impacted the overall estimate. Sensitivity analyses, restricting the study population either to patients without a presumed orthopaedic indication, or to patients with AF, showed consistent estimates, closer to the null than that for the entire population, but still significant for other major bleeding.

In the comparison of our findings with pivotal outcome trials and observational studies, caution is required, as there are differences in the study populations, definitions of bleeding and healthcare systems, as well as other factors that are difficult to take into account. To facilitate comparison with other studies, we show analyses separately for patients with AF and VTE, and for high or low-dose DOAC.

Incidence rates for bleeding events for patients taking warfarin or VKAs highlight the way in which previous observational studies differ from ours, as incidence rates are linked to a number of risk factors. In other words, by comparing incidence rates among patients taking warfarin or VKAs, we thought we could compare background characteristics of the populations under study. Our findings were in line with Danish studies[43,44] as well as with a study in the UK[32] for GI bleeding rates and ICH rates, but our rates were much lower than those reported in studies using US insurance data.[12,23,25]

4.1 | ICH

A recent meta-analysis[30] of observational studies reported a large effect of all 3 DOACs studied on ICH, with relative reductions in incidence of 36% for rivaroxaban, 55% for apixaban, and 58% for dabigatran. There was significant heterogeneity for rivaroxaban. The studies included focused on patients with AF. However, a more recent study,[32] not included in the meta-analysis, showed that the use of rivaroxaban was associated with a lower risk of ICH among patients without AF but not among patients with AF.

4.2 | GI bleeding

In landmark trials,[4–6] dabigatran and rivaroxaban were both associated with a higher rate of GI bleeding than warfarin, whereas

apixaban had a lower rate. Since then, numerous *posthoc* analyses and meta-analyses of these data have concluded that DOACs were likely to involve a higher risk of GI bleeding compared to warfarin, which was related to the use of higher doses, particularly for dabigatran.[45–49] There was no standard definition of GI bleeding in the RCTs, limiting the interpretation of the data, collected as adverse events and coded as such. Moreover, the use of warfarin in the clinical trial setting is likely to be higher than its use in daily practice. Finally, patients enrolled in clinical trials are often not representative of real-world practice. Reports from observational studies using various large administrative datasets have reported contradictory findings,[7,12,14,23,25,26,50] and all have had substantial limitations. Mainly, their data are conditional on the accuracy of administrative coding for diagnoses, and the primary outcome of GI bleeding was not reviewed. One study suggested that the risk of GI bleeding, validated by a manual chart review, was lower with the use of DOACs than with warfarin, irrespective of the indication.[51] More recently, a study in a primary care setting reported that apixaban was associated with a decreased risk of GI bleeding, irrespective of indication.[32] Our study reported no significant difference for either high- or low-dose DOACs compared to VKAs. It is worth noting that not all patients admitted for GI bleeding were categorized as having an outcome because our criteria for major bleeding were more stringent, based on clinical judgement and not solely relying on hospital referral.

4.3 | Other major bleeding events

Few studies have reported on major bleeding events other than ICH and GI bleeding. In a multicentre prospective study, Becattini et al. reported heterogeneous results with significantly more frequent haematuria and upper airway bleeding events and less frequent retroperitoneal and soft/tissue haematomas with DOACs compared to VKAs.[52] A large real-world evaluation in the USA based on elderly Medicare patients with nonvalvular AF reported consistent results across all major bleeding events when comparing apixaban to warfarin, but it also reported some heterogeneity when comparing dabigatran (mostly high-dose) or rivaroxaban to warfarin.[53] A nationwide Norwegian registry study showed a statistically significant reduction in *other* major bleeding events when comparing dabigatran or apixaban (mostly high dose for both) to warfarin.[13] A cohort of patients with nonvalvular AF from a large US commercial database combined with Medicare initiating dabigatran or warfarin treatment showed a statistically significant reduction for other major bleeding events with dabigatran.[26] Definition was based on an algorithm using administrative inpatient claims with either a primary or secondary diagnosis[13,26,53] and these studies reported higher incidence rates than our study. However, our main analysis, combining all DOACs, showed a similar pattern for *other* major bleeding events to that for ICH. In addition, we observed consistent results across the different types of bleeding.

4.4 | Major bleeding and all-cause mortality

A meta-analysis of DOAC trials found a 10% reduction in all-cause mortality with high-dose DOACs compared to warfarin.[49] However, mortality was not significantly different between rivaroxaban and warfarin,[4] whereas the mortality reduction was significant for apixaban (11% reduction)[6] and of borderline significance for high-dose dabigatran.[5] A meta-analysis of observational studies identified 6 studies involving 319 486 patients that compared dabigatran to VKAs with regard to survival and concluded to a significant benefit with dabigatran, but with substantial heterogeneity across studies.[30] Only 1 study involving 41 785 patients reported better survival rates with apixaban than with VKAs.[43] There was no statistical difference between rivaroxaban and VKAs for death in 2 studies that included 51 795 patients.[19,30] There was again significant heterogeneity. Our analysis is in line with these observations, showing a differential effect of DOACs, with better overall survival with high-dose apixaban compared to rivaroxaban or warfarin, whereas there was no substantial difference between high-dose dabigatran and apixaban among patients with AF.

To conclude, our study in real-world practice confirms a clear benefit for DOACs with regard to ICH. It provides new insight into major GI and other major bleeding events, by integrating a medical validation of all bleeding events. While there is reassurance concerning the safety of DOACs for other major non-GI bleeding events, neither dose of DOACs differed significantly from VKAs for major GI bleeding. It is worth noting that incidence rates for major bleeding remained fairly low with DOACs and the numbers needed to observe 1 ICH or 1 other major bleeding event remained fairly large. Lastly, there was a substantial benefit of DOACs in relation to all-cause mortality.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

J.B., E.O. and E.N. participated in the analysis and interpretation of the data and the drafting of the manuscript. J.B. and E.O. participated in the study concept and design. J.B., E.O., E.N., F.B., M.M., L.P., P.M.R., K.L. and L.M.S. participated in the critical revision of the report. E.N., F.B. participated in the statistical analyses.

DATA AVAILABILITY STATEMENT

The statistical code is available from the corresponding author. Under French law and regulations, patient-level data from SNIIRAM cannot be made available.

DATA ACCESS AND CLEANING METHODS

The authors J.B., F.B., E.N. and E.O. had full access to all of the data (extracted from SNIIRAM and clinical database) that was used to generate the study population. The database extracted was stored locally in a dedicated and secure data centre: extraction was performed by CNAMTS; csv data files were imported into the MySql database with a physical data model consistent with the original SNIIRAM database design; investigators had no direct access to SNIIRAM. Metrics and visual tools were used to check data completeness and fit to expected data extraction: the metrics included the number of patients extracted (compared to the expected number), and the stability of reimbursement frequencies over time in order to validate data completeness at a population level.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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